



09/343001

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
--------------------	-------------	-----------------------	------------------

06/29/00 YELLIN

M 0014CIP/DIV1  
EXAMINER

THOMAS J. HALEY, JR.  
FRANK S. NEAVE  
1151 AVENUE OF THE AMERICAS  
NEW YORK, NY 10020

CLASSIFICATION PAPER NUMBER

1644 8

1644  
DATE MAILED:

12/19/00

This is a communication from the examiner in charge of your application.  
COMMISSIONER OF PATENTS AND TRADEMARKS

### OFFICE ACTION SUMMARY

- ☒ Responsive to communication(s) filed on 10/2/00
- ☐ This action is FINAL.
- ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

#### Disposition of Claims

- ☒ Claim(s) 1, 102-144 is/are pending in the application.
- Of the above, claim(s) 102, 103, 105 is/are withdrawn from consideration.
- ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- ☒ Claim(s) 1, 104, 106-144 is/are rejected.
- ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- ☐ Claim(s) \_\_\_\_\_ are subject to restriction or election requirement.

#### Application Papers

- ☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- ☐ The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.
- ☐ The proposed drawing correction, filed on \_\_\_\_\_ is ☐ approved ☐ disapproved.
- ☐ The specification is objected to by the Examiner.
- ☐ The oath or declaration is objected to by the Examiner.

#### Priority under 35 U.S.C. § 119

- ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- ☐ All ☐ Some\* ☐ None of the CERTIFIED copies of the priority documents have been
- ☐ received.
- ☐ received in Application No. (Series Code/Serial Number) \_\_\_\_\_
- ☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

\*Certified copies not received: \_\_\_\_\_

- ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

#### Attachment(s)

- ☒ Notice of Reference Cited, PTO-892
- ☒ Information Disclosure Statement(s), PTO-1449, Paper No(s) 1/24/00, 4/17/00
- ☐ Interview Summary, PTO-413
- ☐ Notice of Draftsperson's Patent Drawing Review, PTO-948
- ☐ Notice of Informal Patent Application, PTO-152

-SEE OFFICE ACTION ON THE FOLLOWING PAGES-

### DETAILED ACTION

1. Applicant's election of the species vasculitis in Paper No. 6, filed 10/2/00.

Claims 1 and 102-144 are pending.

Claims 1, 104 and 106-144 read on the elected invention.

Accordingly, claims 102, 103 and 105 are withdrawn from consideration as being directed to a non-elected invention/species.

Claims 2-101 have been canceled previously.

2. Applicant's submission, filed 10/2/00 (Paper No. 6) places this application in compliance with the sequence rules.
3. In view of applicant's Statement Deleting Inventors Under 37 CAR 1.63(d), filed 6/29/99; the inventorship in this nonprovisional application has been changed by the deletion of Thomas and Karpusas. The Inventive entity of the instant application consists of Yellin, Lederman and Chess.
4. The filing date of the instant claims with respect to the recitation of and "chronic inflammatory autoimmune disease" and "vasculitis" is deemed to be the filing date of parent application USSN 08/637,323, i.e. 4/22/96. Priority applications USSN 08/566,238 and 08/567,391 do not appear to provide a written description for "chronic" and "vasculitis" encompassed by the claims of the instant application. If applicant desires priority prior to 4/22/96; applicant is invited to point out and provide documentary support for the priority of the instant claims. Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.
5. Formal drawings have been submitted which comply with 37 CFR 1.84.
6. The Abstract of the Disclosure is objected to because it does not adequately describe the claimed invention. Correction is required. See MPEP 608.01(b).
7. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.  
Applicant is required to identify the nucleotide and amino acid sequences in the specification with SEQ. ID NOS.  
Trademarks should be capitalized or accompanied by the <sup>TM</sup> or ® symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

8. The following is a quotation of the first paragraph of 35 U.S.C. § 112:  
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
9. Claims 1, 104 and 106-144 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

A) Claims 1, 104 and 106-144: "chronic inflammatory autoimmune diseases":

Upon review of the art on treating established immune responses, particularly those of antigen primed immune systems such as autoimmune diseases, encompassed by the claimed methods; the following is noted.

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of immunosuppressive drugs such as costimulatory-based biopharmaceutical drugs can be species- and model-dependent, it is not clear that reliance on the experimental observations of inhibiting certain in vitro or in vivo immune response would be predictive of treating the breadth of autoimmune diseases encompassed by the claimed methods. There is insufficient objective evidence that accurately reflects the relative efficacy of the claimed therapeutic strategies to inhibit chronic inflammatory autoimmune diseases, commensurate in scope with the therapeutic methods encompassed by the claimed methods.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

Bach (TIPS, 14: 213-216, 1993) reiterates these aspects of immunosuppressive therapy of autoimmune diseases with antibodies directed against T cells (see entire document). Although there has been some success with CD4 in psoriasis and perhaps arthritis, Bach clearly indicates that autoimmune disease cannot be considered as a whole and treatment selection must be considered with each disease (page 213, column 3). Also T cell intervention does not have the same sensitivity in each disease. Bach also reviews the art-known resistance of autoimmunity to therapeutic intervention (page 215, column 3).

The claimed methods encompass treating any number of autoimmune diseases. In contrast to acute conditions, the chronic and complicated nature of the targeted disorders encompassed by the claimed methods are diagnosed only after significant tissue damage has occurred and have an ongoing immune response. With respect to treating various inflammatory conditions with CD40-CD40 ligand antagonists in the face of an ongoing or established immune response, the following limitations have been noted.

Stuber et al. (J. Exp. Med. 183: 693-698, 1996; 1449) disclose when anti-gp39 was given after the disease was established, no effect on the disease activity was observed (see entire document, including Abstract and Discussion). Here, Stuber et al. distinguishes between treating acute conditions such as transplant rejection versus chronic conditions such as autoimmune diseases (see Discussion, last paragraph).

Gray et al. (J. Exp. Med. 180: 141-155, 1994; 1449) teaches that the secondary response was not readily blocked by sCD40- $\gamma$ 1 treatment, indicating a relative independence of CD40 ligation of antigen-experienced B cells (see entire document, including Abstract). Here, if sCD40- $\gamma$ 1 were delayed until day 4 of the primary response, mice develop normal and possibly enhance memory responses.

Resetskova et al. (Thyroid 6: 267- 273, 1996) discloses observations on a model to determine the role of interactions between gp39 and CD40 in an established human Graves' disease and showed immunosuppressive effects on humoral response by directly blocking CD40-gp39 interactions in vivo (see entire document). However, this reference also clearly recognizes the limitations of such experimental observations by stating that it is not clear how anti-gp39 would function in an individual with Graves' disease with an intact immune system (page 272, column 2, paragraph 1). Moreover, inhibition of humoral responses achieved by anti-gp39 in this study was only partial and it is not clear if this would lead to complete remission. The dosage necessary to achieve the optimal results shown in this study may be proportionally too high to be practical in the treatment of human autoimmune thyroid disease and might lead to immune compromise.

Biacone et al. (Kidney Int. 48: 458-468 1995; 1449) teach that soluble CD40 fusion protein can inhibit antibody-mediated glomerular disease if provided in a narrow window of early immune response but that this antagonist was not effective in reversing established disease (see entire document, including the Discussion, particularly the last two paragraphs).

Larsen et al. (Transplantation 61: 4-9, 1996; 1449) disclose that the CD40 ligand-specific antibody prolonged allografts, however if the therapy was delayed until postoperative day 5, such therapy failed to prolong graft survival (see entire document, including Abstract). These observations were also contrasted with others who failed to promote T cell unresponsiveness in vivo in other models (see page 8, column 1, paragraph 1).

It is noted that two Biogen Press Releases (10/21/99; 11/2/99) have indicated the halting of ongoing clinical trials, including its application to Factor VIII inhibitor syndrome, transplantation, multiple sclerosis, ITP and lupus nephritis, with Antova, which is the humanized CD40L-specific antibody based upon the instant 5C8 antibody .

Similarly, Seachrist (BioWorld Today 10 (204) : 1,3, 10/25/99) discloses the halting of clinical trials using the humanized CD40-ligand specific antibody Antova. It is noted that this article discloses that a biotech analyst believes that Antova is dead in its present form.

Further a Press Release from IDEC Pharmaceuticals, Inc. (4/20/00) indicates that treating SLE with another anti-CD40L antibody was not significantly different from that observed in the control group where a marked placebo effect was noted and, in turn, the Phase III Development program will not be pursued at this time.

Therefore, the reliance upon observations wherein the CD40 ligand/5C8 antagonists are administered at the same time as initial stimulus or insult may inhibit humoral immune response or immunoglobulin production. Even though subsequent secondary responses may be affected, such observations still rely upon inhibiting activation of T cells at the onset or initiation of experiencing the antigen or stimulus and not upon experiencing an ongoing responses wherein secondary responses or antigen experienced lymphocytes are already in place. In contrast the claimed methods encompass using 5C8-specific antibodies to treat chronic inflammatory autoimmune diseases wherein the diagnosis of such diseases occur after antigen priming has occurred.

CD40-CD40 ligand antagonists appear to inhibit the onset or activation of the immune response. In contrast, CD40-CD40 ligand antagonists do not appear to inhibit an established or ongoing immune or inflammatory responses, encompassed by the claimed methods, as evidenced by the references of record and set forth herein.

Therefore, it is not clear that the skilled artisan could predict the efficacy of the 5C8-specific antibodies, as exemplified in the specification as filed to inhibit autoimmune diseases.

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective antibody-based therapies on inhibiting human transplant rejection, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent a sufficient number of working examples providing evidence which is reasonably predictive that the claimed methods are effective for inhibiting human autoimmunity with 5C8-specific antibodies.

B) Claims 118-119: Mammal/non-human primate:

Applicant has not enabled 5C8/CD40L-specificity for all of the species set forth in claims 118-119. While CD40L has been identified in mice and humans; there is insufficient direction and guidance in the specification as filed to enable all of the mammalian and non-human species encompassed by the claimed methods.. Applicant has not provided sufficient biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies the 5C8/CD40L specificity in the breadth of mammalian and non-human species recited in claims 118-119. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

C) Claims 141-144:

"gene therapy vectors", "therapeutic agents", "antigenic pharmaceuticals" and "blood products":

There appears to be insufficient guidance and direction in the specification as filed for providing for these concepts together and, in particular, coadministration of a compound of the invention along with a gene therapy vector or a therapeutic agent as a dependent claim of treating vasculitis.

There is insufficient direction or guidance provided to assist one skilled in the art in the selection of such "gene therapy vectors", "therapeutic agents", "antigenic pharmaceuticals" and "blood products" nor is there sufficient evidence provided how such "gene therapy vectors", "therapeutic agents", "antigenic pharmaceutical" and "blood products" could be used in methods to "treat vasculitis". It would require undue experimentation to produce all such possible "gene therapy vectors", "therapeutic agents", "antigenic pharmaceutical" and "blood products" without more explicit guidance from the disclosure. It would require undue experimentation to investigate all such "gene therapy vectors", "therapeutic agents", "antigenic pharmaceutical" and "blood products". It is not readily apparent from the claimed invention how these "gene therapy vectors", "therapeutic agents", "antigenic pharmaceuticals" and "blood products" are involved in the claimed methods to "treat vasculitis". Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. It appears that undue experimentation would be required of one skilled in the art to practice the claimed methods to "gene therapy vectors", "therapeutic agents", "antigenic pharmaceuticals" and "blood products". commensurate in scope with the claimed invention using the teaching of the specification.

For example, it is noted that the claimed invention encompasses in vivo gene therapy in vasculitis. This art is currently plagued with high level of unpredictability. For example, efficient delivery and expression of foreign DNA had not yet been achieved by any method. There has been no unambiguous evidence that treatment has produced therapeutic benefits and that difficulties in getting genes transferred efficiently to target cells - and getting them expressed - remain a nagging problem for the entire field.

A major problem associated with gene therapy has been poor delivery of the gene therapy agent to target cells *in vivo*. The gene therapy art is replete with examples of gene therapy vehicles which deliver gene therapy agents efficiently to target cells *in vitro* but inexplicitly fail to target the appropriate cells *in vivo* (for reviews of the unpredictability of the gene therapy art, see Anderson, (Nature, 392: 25-30, 1998); Verma et al. (Nature, 389: 239-242, 1997); Ross et al. (Human Gene Therapy, 7: 1781-1790, 1996). *In vivo* or therapeutic regulation of immune responses with naked nucleic acid vaccines or recombinant cell vaccines have been limited and unpredictable. Although there have been some success in achieving gene expression, the problems of efficient delivery systems, lack of sustained expression and host immune reactions remain formidable challenges to gene therapy, as known in the art and evidenced by Verma et al., including the lack of good enhancer-promoter combinations which allow for the sustained effective production of protein (Nature, 1997; see entire document, including first paragraph). Given the limited information in the specification as filed; it is therefore concluded that in light of the quantity of experimentation necessary, the lack of adequate direction or guidance presented, the lack of correlatable working examples, the nature of the invention, the state of the prior art with its recognized unpredictability, and the breadth of the claims, it would require undue experimentation for others skilled in the art to practice the invention.

It is therefore concluded that in light of the quantity of experimentation necessary, the lack of adequate direction or guidance presented, the lack of correlatable working examples, the nature of the invention, the state of the prior art with its recognized unpredictability, and the breadth of the claims, it would require undue experimentation for others skilled in the art to practice the invention.

It is noted that systemic vasculitis represent a heterogenous set of disorders. Luqmani et al. (Scand J. Rheumatol. 29: 211-215, 2000) discloses that it is unlikely that there will ever a large randomized placebo controlled trials to establish the effectiveness of current therapeutic regimens and that the best available evidence will be from long term observational studies, uncontrolled trials and randomized but non-placebo controlled trials (see entire document, including Abstract, Introduction). Luqmani concludes that specific therapies are available in some types of vasculitis but the majority of cases, non-specific interference with the immune system is most appropriate (page 214, Conclusions).

Applicant has not provided sufficient biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies "gene therapy vectors", "therapeutic agents", "antigenic pharmaceuticals" and "blood products to use in combination with CD40L-specific antibodies to treat vasculitis. While these "limitations" may have some notion of the activity of the "various agents, vectors, pharmaceuticals, products"; claiming biochemical molecules in this manner only fails to enable the skilled artisan to make and use the scope of such "products" nor is there is insufficient guidance and direction as to structure of the "products", broadly encompassed by the claimed invention.

The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 18 24 (CCPA 1970).

"It is not sufficient to define the recombinant molecule by its principal biological activity, e.g. having protein A activity, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property." Colbert v. Lofdahl, 21 USPQ2d, 1068, 1071 (BPAI 1992).

The specification does not describe nor enable for the skilled artisan on how to make and use any "gene therapy vectors", "therapeutic agents", "antigenic pharmaceuticals" and "blood products" in the treatment of vasculitis. Since the amino acid sequence of a molecule/polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a molecule's structure and still retain similar functionality requires a knowledge of and guidance with regard to the structure (e.g. amino acids in the polypeptide's sequence), if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which a molecule's structure relates to its functional usefulness. For example, the problem of predicting the structure of a molecule other than the structure of a bispecific antibody and, in turn, utilizing predicting structural determinations or functional attributes of the claimed "products" to be employed in the claimed methods to treat vasculitis is complex and outside the realm of routine experimentation. The more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. See MPEP 2164.03.

It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions can result in substantially different biological or pharmacological activities.

Because of the lack of sufficient guidance and predictability in determining on how to make and use any "gene therapy vectors", "therapeutic agents", "antigenic pharmaceuticals" and "blood products"; it would require an undue amount of experimentation for one of skill in the art to arrive at the claimed methods to treat vasculitis with reagents in combination with the claimed CD40L-specific antibodies. Without sufficient guidance, making and using any "gene therapy vectors", "therapeutic agents", "antigenic pharmaceuticals" and "blood products" in the claimed methods is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue

D) Given the availability of the 5C8 antibody produced by the hybridoma designated as ATCC as evidenced by U.S. Patent No. 5,474,771 (of record); the 5C8 antibody is considered enabled.

10. Claims 1, 104 and 106-144 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention essentially for the reasons set forth in the previous Office Actions (Paper Nos. 22/25).

A) Claims 1, 104 and 106-144 are indefinite in the recitation of "and a portion thereof" because it is not clear which portion is being referred to and the metes and bounds are not defined. Even in the claims reciting "comprises a Fab ..."; the recitation of "comprises" opens the claim to include other elements not clearly defined or disclosed.

B) It is noted that page 27, paragraph 2 of the specification provides for the written support for coadministration of a compound of the invention along with a gene therapy vector or a therapeutic agent such as an antigenic pharmaceutical or a blood product in the specification as filed is in the context of preventing an immune response to an antigen.

There appears to be insufficient guidance and direction in the specification as filed for providing for these concepts together and, in particular, coadministration of a compound of the invention along with a gene therapy vector or a therapeutic agent as a dependent claim of treating vasculitis, as pointed out above.

Therefore, the instant claims 141-144 are indefinite in the recitation of "administered with a gene therapy vector or a therapeutic agent" because the intention of the claim in the context of "treating vasculitis" is unclear. Also, the characteristics of the "gene therapy vector", "therapeutic agent", antigenic pharmaceutical" and "blood products" are vague and indefinite since they encompass a myriad of different "vectors", "pharmaceuticals" "agents" and "products" and it is not apparent from the disclosure which particular "gene therapy vectors", "therapeutic agents", "antigenic pharmaceuticals" and "blood products" are being referred to.

Applicant has not provided sufficient information that distinctly identifies the "gene therapy vector", "therapeutic agents", "antigenic pharmaceuticals" and "blood products" encompassed by the claimed methods to "treat vasculitis". The recitation of "gene therapy vector", "therapeutic agents", "antigenic pharmaceuticals" and "blood products" fails to distinctly claim what these molecules/compositions are or what they are made up of. Therefore, there is insufficient information and guidance for the metes and bounds of the "gene therapy vectors", "therapeutic agents", "antigenic pharmaceuticals" and "blood products" encompassed by the claimed methods.

C) The applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

13. For examination purposes, vasculitis broadly refers to inflammation of a vessel.

See The Merck Manual Sixteenth Edition of Diagnosis and Therapy, 1992; pages 1315-1316.

Given the number of copending applications, applicant is invited to clarify whether inhibiting vasculitis reads on other therapeutic endpoints. For example, applicant is invited to clarify whether inhibiting vasculitis reads on inhibiting other inflammatory conditions, such as transplant rejection, ischemia and reperfusion or particular autoimmune conditions. Therefore, issues of double patenting are held in abeyance until applicant clarifies the scope of the instant elected invention and how it reads on copending applications and claimed limitations.

14. Claims 104 and 106-144 are rejected under 35 U.S.C. § 102(e) as being anticipated by Noelle et al. (U.S. Patent No. 5,683,693; 1449) (see entire document). Noelle et al. teaches methods of inhibiting tissue/organ rejection with CD40L-specific antibodies (e.g. gp39-specific and 5C8-specific antibodies), including the use of recombinant antibodies and fragments (columns 5-7) in conventional methods including various dosages and modes of administration (columns 8-11) as well as the use of antigen-presenting cells (e.g. blood products, antigenic pharmaceuticals) (see entire document, including the claims). Also, Noelle et al. teaches the ability of these CD40L-specific antibodies to inhibit T cell responses and CD40L interactions with other cell types including B cells and endothelial cells (columns 7-8). Given the role of T cells in graft rejection including transplantation and that , the graft microvascular endothelia express an inflamed phenotype associated with wound healing and the repair of tissue damage due to mechanical trauma; inhibiting vasculitis would be inherent in the method taught and claimed by Noelle et al. to induce T cell unresponsiveness in graft rejection with CD40L-specific antibodies. Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations addressed by the applicant would be inherent properties of the referenced methods/antibodies. Also, see Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. V. Milgram, 52 USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999).

144a 15. Claims 1, 104-138 are rejected under 35 U.S.C. § 102(e) as being anticipated by Black et al. (U.S. Patent No. 6,001,358) (see entire document). Black et al. teaches methods of inhibiting tissue/organ rejection and GVHD (columns 31-34) and vasculitis (column 33, line 64) with CD40L-specific antibodies (e.g. gp39-specific and 5C8-specific antibodies), including the use of recombinant antibodies and fragments (columns 13-22) in conventional methods including various dosages and modes of administration to meet the needs of the patient and the nature of the disease or condition (columns 34-38). In addition to treating vasculitis; given the nature of graft rejection including transplantation and GVHD and that, the graft microvascular endothelia express an inflamed phenotype associated with wound healing and the repair of tissue damage due to mechanical trauma; inhibiting vasculitis would be inherent in the referenced methods. Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations addressed by the applicant would be inherent properties of the referenced methods/antibodies. Also, see Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. V. Milgram, 52 USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999).

16. Claims 1, 104 and 106-144 are rejected under 35 U.S.C. § 103 as being unpatentable over Noelle et al. (U.S. Patent No. 5,683,693; 1449) AND/OR Black et al. (U.S. Patent No. 6,001,358) in view of Lederman et al. (WO 93/09812; 1449), Morgan et al. (Transplantation 55: 919-923, 1993) and Haug et al. (Transplantation 55: 766-773, 1993).

Noelle et al. teaches methods of inhibiting tissue/organ rejection with CD40L-specific antibodies (e.g. gp39-specific and 5C8-specific antibodies), including the use of recombinant antibodies and fragments (columns 5-7) in conventional methods including various dosages and modes of administration (columns 8-11) as well as the use of antigen-presenting cells (e.g. blood products, antigenic pharmaceuticals) (see entire document, including the claims). Also, Noelle et al. teaches the ability of these CD40L-specific antibodies to inhibit T cell responses and CD40L interactions with other cell types including B cells and endothelial cells (columns 7-8). Noelle et al. differs from the instant claims by not disclosing the effects of this treatment on reperfusion injury per se.

Black et al. teaches methods of inhibiting tissue/organ rejection and GVHD (columns 31-34) and vasculitis (column 33, line 64) with CD40L-specific antibodies (e.g. gp39-specific and 5C8-specific antibodies), including the use of recombinant antibodies and fragments (columns 13-22) in conventional methods including various dosages and modes of administration to meet the needs of the patient and the nature of the disease or condition (columns 34-38)

Lederman et al. (WO 93/09812) teach the inhibition of various immune cell interactions associated with 5C8 via 5C8-specific antibodies, including recombinant antibodies and methods of screening for said antibodies (see entire document) The referenced 5C8 antigen specificity was also known as CD40L at the time this publication was available

Morgan et al. teach the role of T cells in graft rejection including after transplantation, the graft microvascular endothelia express an inflamed phenotype associated with wound healing and the repair of tissue damage due to mechanical trauma, ischemia and or reperfusion injury after transplantation (see Abstract and Discussion)

Haug et al. teach the inhibition of leukocytes with antibody therapy could be useful in controlling allograft rejection and limiting reperfusion injury (see Abstract and Discussion). Haug et al. teach the use of anti-ICAM-1 antibodies to inhibit both the stimulatory and effector stages of T cell mediated graft rejection.

Given the teachings that inhibiting T cell-mediated responses in graft rejection would be beneficial with respect to reperfusion injury; it would have been expected that the methods taught by Noelle et al. And Black et al. Would have resulted in inhibiting vasculitis associated with transplantation. Also, the claimed effects on transmigration would have been expected given the ability to inhibit CD40L-mediated responses including the inhibition of graft rejection, and in turn, the inhibition of vasculitis.

It was well known and practiced at the time the invention was made to make and modify antibodies for human use, including the generation of various antigen-binding fragments (e.g. Fab, single chain antibody) as well as recombinant antibodies (e.g. chimeric, humanized and primatized) encompassed by the claimed methods. It was art known methods to employ recombinant forms of antibodies to increase half-life and efficacy of antibody-mediated therapies and to screen antibodies of interest.

It was well known and practiced at the time the invention was made that inhibiting graft rejection required the administration of other therapeutic agents to prevent and maintain graft survival. Although CD40L-specific antibodies could be used to diminish the reliance on conventional therapeutic intervention including immunosuppression in such modalities; the administration of combination therapies as well as additional therapeutic agents was known and required at the time the invention was made. In addition, given the breadth of therapeutic agents/blood products; the use of other inhibitory antibodies such as anti-CD3 or antibody preparations such as anti-lymphocyte serum or the use of blood-derived cells or elements in transplant regimens known and practiced at the time the invention was made would be encompassed by the claimed methods. Note that Noelle et al. teaches the use of antigen-presenting cells in therapeutic modalities (see entire document).

In addition to the dosages and modes of administration as taught by Noelle et al. , Black et al. and Lederman et al.; the claimed dosages and routes of administration were known and practiced at the time the invention was made and/or would have been encompassed in providing for sufficient therapeutic intervention depending on the patient's needs at the time the invention was made.

Therefore, the combined teachings teach targeted inflammatory conditions including those that involve the fibrotic diseases by inhibiting CD40-CD40L interactions with CD40L-specific antibodies. Therefore, it would have obvious to employ such methods to target mammalian diseases or disease models that involve the various inflammatory conditions, targeted and encompassed by the claimed methods. It was known at the time the invention was made to employ recombinant antibodies and antibody fragments to increase half-life and efficacy of antibody-mediated therapies. The references also guide the ordinary artisan to downregulate inflammatory conditions associated with fibrosis with CD40L-specific antibodies. Also, the generation of recombinant antibodies such as chimeric, humanized and primatized as well as standard antibody screening procedures as well as modes of administration were all well known in the art at the time the invention was made.

One of ordinary skill in the art at the time the invention was made would have been motivated to select the ability of CD40L-specific antibodies to inhibit graft rejection and, in turn, to expect or to apply such modalities to inhibit vasculitis. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

17. Claims 141-144 are rejected under 35 U.S.C. § 103 as being unpatentable over Noelle et al. (U.S. Patent No. 5,683,693; 1449) AND/OR Black et al. (U.S. Patent No. 6,001,358) in view of Lederman et al. (WO 93/09812), Morgan et al. (Transplantation 1993) and Haug et al. (Transplantation, 1993) As applied to claims 1, 104-144 above and in further view of Humphries et al. (U.S. Patent No. 5,804,177).

Noelle et al., Black et al., Lederman et al., Morgan et al. And Haug et al. are taught above and differ from the claimed methods by not disclosing gene therapy vectors.

Humphries et al. teach the use of recombinant vectors to express MHC antibodies to induce immunological tolerance or non-responsiveness (see column 13, paragraph 3). Given the breadth of gene therapy vectors and antigenic pharmaceuticals; the referenced vectors employed in methods to induce immunological non-responsiveness as taught by Noelle et al. would be encompassed by the claimed gene therapy vectors antigenic pharmaceuticals.

One of ordinary skill in the art at the time the invention was made would have been motivated to select the use of recombinant vectors to aid in inducing immunological non-responsiveness together with ability of CD40L-specific antibodies to promote graft acceptance and, in turn, to expect or to apply such modalities to inhibit reperfusion injury. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

18. No claim is allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

*Phillip Gambel*

Phillip Gambel, PhD.  
Primary Examiner  
Technology Center 1600  
December 18, 2000